Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 9, 10, and 12-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description in that the disclosure does not reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The Office Action alleges that the specification does not provide support for the claims "having greater than 88%/79% identity."

The Office Action alleges that there is insufficient written description for several phrases, including "greater than," "at least one LM609 CDR-grafted heavy/light chain polypeptide comprising a variable region amino acid sequence greater than 88%/79% identity with that shown in Figure 1A/1B," "functional fragments" thereof, or "nucleic acids" encoding the same. Applicant wishes to clarify that claim 1 was amended in the previous response mailed June 7, 2000, such that the phrase "greater than" is no longer recited in the claim. Claim 1 recites "at least one LM609 CDR-grafted heavy chain polypeptide comprising a variable region amino acid sequence shown in Figure 1A (SEQ ID NO:2), said variable region amino acid sequence having a framework sequence <u>having 88% or greater identity</u> with the framework sequence of SEQ ID NO:2, and at least one LM609 CDR-grafted light chain polypeptide comprising a variable region amino acid sequence shown in Figure 1B (SEQ ID NO:4), said variable region amino acid sequence having a framework sequence <u>having 79% or greater identity</u> with the framework sequence of SEQ ID NO:4" (emphasis added).

Applicant respectfully submits that the specification provides sufficient written description to convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. The claims are directed to a LM609 CDR-grafted antibody and a LM609 CDR-grafted heavy or light chain polypeptide, or encoding nucleic acids, having a framework sequence having 88% or greater identity with SEQ ID NO:2 or 79% or greater identity with SEQ ID NO:4, respectively.

In particular, the specification teaches that the human heavy chain variable region M72 'CL had 88% identity with frameworks 1, 2 and 3 of LM609 heavy chain and that the human light chain V region LS1 'CL had 79% identity to frameworks 1, 2 and 3 of LM609 light chain (page 45, lines 5-8). These framework sequences were used to generate LM609 CDR-grafted heavy and light chain variable region amino acid sequences shown in Figures 1A and 1B (pages 45-48). The specification also teaches LM609 grafted heavy and light chain polypeptides or functional fragments thereof, where the LM609 grafted heavy chain polypeptide exhibits substantially the same amino acid sequence as that shown in Figure 1A (SEQ ID NO:2) and the LM609 grafted light chain exhibits substantially the same amino acid sequence as that shown in Figure 1B (SEQ ID NO:4), as well as encoding nucleic acids (page 14, line 24, to page 15, line 3; page 25, lines 9-21).

The specification further teaches the nature of modifications of LM609 grafted antibodies. In particular, the specification teaches that substitution of amino acid residues

outside of the Kabat CDRs can additionally be performed to maintain or augment beneficial binding properties of LM609 grafted antibodies so long as such amino acid substitutions do not correspond to a donor amino acid at that particular position (page 15, lines 21-26). The specification additionally teaches that minor modifications of LM609 grafted heavy and light chain nucleotide sequences are included as LM609 grafted heavy and light chain encoding nucleic acids and their functional fragments (page 17, lines 21-24). The specification provides teachings on the nature of the minor modifications and that such minor modifications of the LM609 grafted antibody encoding nucleotide sequences allow for the functional replacement of amino acids (page 17, line 21, to page 18, line 29). The specification also teaches methods of substituting functionally equivalent amino acids encoded by LM609 grafted antibody nucleotide sequences by identifying the amino acids which are desired to be changed, incorporating the changes and then determining the function of the recombinantly expressed and modified LM609 grafted polypeptide (page 18, line 24, to page 19, line 14). The specification also teaches exemplary methods for making such substitutions, including codon based mutagenesis, random oligonucleotide synthesis and partially degenerate oligonucleotide synthesis (page 19, line 14, to page 20, line 15).

Furthermore, the specification teaches that these methods can be used to change any or all of the non-identical amino acids either alone or in combination with amino acids at different positions to incorporate the desired number of amino

acid substitutions at the desired positions (page 20, lines 22-27). The specification additionally teaches that the LM609 grafted polypeptides containing the desired substituted amino acids are produced and screened for retention or augmentation of function compared to the unsubstituted LM609 grafted polypeptides and that such substituted polypeptides are considered to contain minor modifications of the encoding nucleotide sequence (page 20, line 27, to page 21, line 10). The specification further teaches that all non-identical amino acid residues between the donor and the human framework can be identified and substituted with any or all other possible amino acid residues, excluding the corresponding donor amino acid, at each non-identical position to produce a population of substituted polypeptides containing all possible or all desired permutations or combinations (page 21, lines 21-29).

Accordingly, based on the teachings in the specification, one skilled in the art would have understood that any or all of the non-identical amino acids that differ between the human framework and LM609 heavy chain can be modified. Since the specification teaches that the human framework sequence of Figure 1A and LM609 heavy chain are 88% identical (page 45, lines 5-8), one skilled in the art would have understood that substitution of all of the 12% non-identical amino acids would result in a heavy chain polypeptide variable region amino acid sequence having a framework sequence having 88% identity to the human framework sequence of SEQ ID NO:2. One skilled in the art similarly would have understood that substitution of any, but less than all, of the 12% non-identical amino acids would result

in a heavy chain polypeptide variable region amino acid sequence having a framework sequence having greater than 88% identity. Accordingly, one skilled in the art would have understood that the specification teaches a variable region amino acid sequence having a framework sequence having 88% or greater identity with the framework sequence of SEQ ID NO:2, as claimed. Since the specification teaches that the human framework sequence of Figure 1B and LM609 light chain are 79% identical, one skilled in the art would have understood that substitution of any or all of the 21% non-identical amino acids would result in a light chain polypeptide variable region amino acid sequence having a framework sequence having 79% or greater identity with the framework sequence of SEQ ID NO:4, as claimed.

Applicant respectfully disagrees with the assertion in the Office Action that the specification as filed does not provide sufficient written description "for these newly claimed limitations." The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. In re Kaslow, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed. Cir. 1983); Eiselstein v. Frank, 52 F.3d 1035, 34 U.S.P.Q.2d 1467 (Fed. Cir. 1995).

> This is the essence of the description requirement of section 112, first paragraph: whether one skilled in the art, familiar with the practice of the art at the time of the

> filing date, could reasonably have found the "later" claimed invention in the specification as filed.

Texas Instruments v. U.S. International Trade Commission, 871 F.2d 1054, 1062, 10 U.S.P.Q.2d 1257, 1263 (Fed. Cir. 1989).

The specification need not provide literal support for the claim language but, rather, convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed. In re Kaslow, *supra*.

> The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material.... It is not necessary that the application describe the claim limitations exactly..., but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.

In re Wertheim, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976) (citations omitted). Furthermore, the teachings in the entire specification must be considered.

> When the scope of a claim has been changed by amendment in such a way as to justify an assertion that it is directed to a *different invention* than was the original claim, it is proper to inquire whether the newly claimed subject matter was *described* in the patent application when filed as the invention of

> the applicant.... In deciding the issue, the specification as a whole must be considered.

In re Wright 866 F.2d 422, 424-425, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1988)(emphasis in original).

Applicant respectfully submits that, based on the teachings in the specification and for the reasons described above, one skilled in the art would have understood that Applicant was in possession of the claimed invention at the time the application was filed. In particular, one skilled in the art would have understood that Applicant was in possession of the claimed LM609 CDR-grafted antibody having a framework sequence having 88% or greater identity with the framework sequence of SEQ ID NO:2 and a framework sequence having 79% or greater identity with the framework sequence of SEQ ID NO:4, as recited in the claim.

In regard to functional fragments of the claimed LM609 CDR-grafted antibodies and heavy and light chain polypeptides, the specification teaches that a functional fragment is a portion of a LM609 grafted antibody including heavy or light chain polypeptides which still retains some or all of the $\alpha_v\beta_3$ binding activity, $\alpha_v\beta_3$ binding specificity and/or integrin $\alpha_v\beta_3$-inhibitory activity (page 14, lines 4-10). In regard to the nucleic acids, the specification teaches that the invention provides a nucleic acid encoding a heavy chain and light chain for a LM609 grafted antibody (page 14, line 24-28). The claims reciting 88% or 79% identity with the framework sequence of a specifically recited SEQ ID NO also recite functional characteristics of an antibody

containing a polypeptide encoded by the nucleic acid, specifically that the antibody has integrin $\alpha_v\beta_3$ binding activity, integrin $\alpha_v\beta_3$ binding specificity, or integrin $\alpha_v\beta_3$-inhibitory activity. Such functional activities of the antibody are specifically recited in the claims and, in regard to modification of non-identical residues in a human framework sequence relative to LM609, the specification teaches that the LM609 CDR-grafted polypeptides containing desired substitutions of non-identical amino acids can be screened for activity (page 20, line 22, to page 21, line 1, and page 21, line 21, to page 22, line 1). Accordingly, Applicant respectfully maintains that the specification provides sufficient description for "functional fragment" and "nucleic acids," as recited in the claims.

Applicant respectfully maintains that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(f)

Claims 1-18 and 26-31 stand rejected under 35 U.S.C. § 102(f) because Applicant allegedly did not invent the claimed subject matter. The Office Action alleges that Applicant's arguments in conjunction with the Huse Declaration filed in the response mailed December 9, 1998, U.S. Patent No. 5,753,230, issued May 19, 1998 (Brooks et al.), and the Biotechnology

Newswatch article dated January 16, 1995, presents an ambiguity with regard to the inventorship of the claimed invention.

As stated previously, inventorship was reviewed and determined to be correct. Applicant respectfully disagrees with the assertion in the Office Action on page 3, section 5, paragraph 4, that Drs. Huse and Glaser have been determined to be inventors of the claimed compositions. Dr. Huse has been determined to be the inventor in the above-identified application. Dr. Huse and Dr. Glaser have been determined to be joint inventors in application serial No. 08/791,391. In regard to Dr. Huse and Dr. Glaser being named as joint inventors of co-pending application serial No. 08/791,391, Applicant points out that the claims in the present application are not identical to the claims pending in application serial No. 08/791,391, and inventorship has been determined not to be identical in the two applications.

Regarding the Declaration by Dr. Huse submitted as Exhibit 1 with the response mailed December 9, 1998, this previously filed Declaration was directed to the issue of alleged public use or on sale activity, not to inventorship. Although Dr. Huse states that "I conceived the idea of humanizing $\alpha_v\beta_3$ inhibitory antibodies," the Declaration does not address inventorship of the claimed compositions having specifically recited SEQ ID NOS. Therefore, the Declaration by Dr. Huse submitted on December 9, 1998, in no way presents ambiguity regarding inventorship of the claimed invention.

Applicant respectfully points out that, in contrast to the assertion in the Office Action on page 3, section 5, paragraphs 3 and 5, no Declaration by Dr. Huse and Dr. Glaser was filed in the present application in the response mailed September 20, 1999, or June 7, 2000.

In regard to the Declaration by Dr. Huse submitted as Exhibit 1 with the previous response mailed June 7, 2000, this Declaration avers to Dr. Huse's inventorship of the present application. The Declaration states that the LM609 hybridoma was brought to Ixsys, Inc., where the LM609 heavy and light chain variable region cDNA was cloned. Dr. Huse also avers in the Declaration that the sequences of the claimed antibodies and encoding nucleic acids were not known prior to cloning and sequencing of the LM609 heavy and light chain variable region and generation of LM609 grafted antibodies at Ixsys.

Applicant maintains that, based on the evidence of record, only Dr. Huse can properly be named as the inventor in view of the position of the Federal Circuit with respect to inventorship. Firstly, the inventor is the person or persons who conceived the patented invention. Collar Co. v. Van Dusen, 90 U.S. (23 Wall.) 530, 563-564, 23 L.Ed. 128 (1874); Burroughs Wellcome Co. v. Barr Lab., Inc., 40 F.3d 1223, 1227-1228, 32 U.S.P.Q.2d 1915, 1919 (Fed. Cir. 1994); C.R. Bard Inc. v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998). Secondly, for certain inventions, including nucleic acids, conception occurs simultaneously with reduction to practice. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d

1200, 18 U.S.P.Q.2d 1016 (Fed Cir. 1991); Hitzeman v. Rutter 243 F.3d 1345, 58 U.S.P.Q.2d 1161 (Fed. Cir. 2001). Conception of a nucleic acid sequence has been addressed by the Federal Circuit in Amgen. The Federal Circuit held:

> We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.

Id. at 1206, 18 U.S.P.Q. at 1021.

Consistent with the holding in Amgen, Applicant maintains that conception of the claimed compositions having specifically recited SEQ ID NOS requires the determination of the nucleotide sequence of LM609 heavy and light chain variable regions and the use of the determined sequences to generate the claimed grafted antibodies having specifically recited SEQ ID NOS. As stated in the Declaration by Dr. Huse submitted as Exhibit 1 in the response mailed June 7, 2000, the nucleotide sequence of LM609 was determined at Ixsys, Inc., and LM609 CDR-grafted antibodies were generated and developed.

Regarding Dr. Cheresh and Dr. Brooks, the Declaration submitted as Exhibit 1 in the response mailed June 7, 2000, clearly indicates that neither Dr. Cheresh nor Dr. Brooks suggested or contributed to the cloning, sequencing, humanizing or making of the claimed antibodies and nucleic acids. In view

of the Federal Circuit holding in Amgen, Applicant maintains that, absent an inventive contribution by Drs. Cheresh or Brooks to the cloning, sequencing, humanizing or making of the claimed antibodies and nucleic acids, neither Dr. Cheresh nor Dr. Brooks can be considered an inventor of the claimed compositions having specifically recited SEQ ID NOS.

The Office Action continues to assert that it was possible to determine, without undue experimentation, antibodies and humanized antibodies having the same properties as LM609 and that U.S. Patent No. 5,753,230 claims the use of LM609 antibody and humanized versions thereof. Applicant maintains that any description of a humanized LM609 in U.S. Patent No. 5,753,230 is a statement of a problem to be solved because there is no completion of the mental part of the invention. Significantly, U.S. Patent No. 5,753,230 provides no description of any nucleotide or amino acid sequence of LM609 or humanized LM609 and, as such, lacks a description of a definite and permanent idea of the complete and operative invention. Coleman v. Dines, 754 F.2d 353, 359, 224 U.S.P.Q. 857, 862 (Fed. Cir. 1985); Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1227-1228, 32 U.S.P.Q.2d 1915, 1919 (Fed. Cir. 1994). Similarly, the Biotechnology Newswatch article published January 16, 1995, which has been asserted in the Office Action as allegedly raising ambiguity with respect to inventorship, provides no description of any nucleotide or amino acid sequence of LM609 or humanized LM609 and therefore lacks a description of a definitive and permanent idea of the complete and operative invention. The Biotechnology Newswatch article similarly does not raise an issue

of ambiguity with respect to inventorship because the Biotechnology Newswatch article clearly states that the rights to modify the antibody LM609 have been licensed to Ixsys, Inc. and that the company, Ixsys, Inc., has developed a humanized version of LM609. These statements are consistent with the arguments and evidence of record, that the sequences of the claimed LM609 grafted antibodies were invented at Ixsys.

Further regarding conception of nucleic acids and the assertion in the Office Action of the alleged lack of undue experimentation required to determine antibodies and humanized antibodies having the same properties as LM609 in view of U.S. Patent No. 5,753,230, Applicant contends that the Federal Circuit has determined it is irrelevant whether the method for obtaining a nucleotide sequence is simple or complex, absent a teaching of the nucleotide sequence of LM609 or the nucleotide or amino acid sequence of LM609 CDR-grafted antibodies. The Federal Circuit in Fiers v. Revel, 984 F.2d 1164, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993), determined that, based on previous federal court decisions, the applicable rule of law states that:

> [I]rrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility.

Id. at 1169, 25 U.S.P.Q. at 1604. Since U.S. Patent No. 5,753,230 provides no teaching or suggestion of the nucleotide or amino acid sequence of LM609 or humanized versions

thereof and since neither Dr. Cheresh nor Dr. Brooks suggested or contributed to the cloning, sequencing, humanizing or making of the claimed antibodies and encoding nucleic acids, neither Dr. Cheresh nor Dr. Brooks can be considered inventors of the claimed compositions having specifically recited SEQ ID NOS. Accordingly, Applicant maintains that the determination that Dr. Huse is the inventor and that neither Dr. Cheresh nor Dr. Brooks can be considered inventors of the claimed compositions is proper.

In summary, Applicant maintains that Dr. Huse is the inventor of the claimed compositions. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

Claim 26 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Brooks et al., U.S. Patent No. 5,753,230. Applicant maintains that claim 26 is novel over Brooks et al.

Claim 26 is directed to a LM609 CDR-grafted antibody comprising a LM609 CDR-grafted heavy chain polypeptide encoded by a LM609 CDR-grafted heavy chain variable region nucleotide sequence referenced as SEQ ID NO:1, or a modification thereof, and a LM609 CDR-grafted light chain polypeptide encoded by a LM609 CDR-grafted light chain variable region nucleotide sequence referenced as SEQ ID NO:3, or a modification thereof, having integrin $\alpha_V\beta_3$ binding activity, integrin $\alpha_V\beta_3$ binding specificity

or integrin $\alpha_v\beta_3$-inhibitory activity. In contrast, Brooks et al. does not teach the claimed human acceptor framework sequences with LM609 CDRs encoded by the specifically recited nucleotide sequences referenced as SEQ ID NOS:1 and 3.

To anticipate a claim, the reference must teach every element of the claim. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989); In re Spada, 15 U.S.P.Q.2d 1655 (Fed. Cir. 1990). "[A]ll limitations in the claims must be found in the reference since the claims measure the invention." In re Lange, 644 F.2d 856, 862, 209 U.S.P.Q. 288, 293 (C.C.P.A. 1981).

Accordingly, absent a teaching of every element of the claimed invention, that is, absent a teaching of the structural features of the antibody specifically recited in the claim as SEQ ID NOS:1 and 3, Applicant respectfully submits that Brooks et al. cannot anticipate the claim. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1-18 and 26-31 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Brooks et al., U.S. Patent No. 5,753,230, in view of the known art of gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. Applicant respectfully maintains that the claimed compositions directed to an antibody comprising a

variable region amino acid sequence referenced as SEQ ID NOS:2 and 4 and encoding nucleic acids are unobvious over Brooks et al.

Applicant respectfully maintains that, for the reasons of record set forth in Applicant's previous responses mailed March 3, 1998, December 9, 1998, September 20, 1999, and June 7, 2000, at least two of the requirements to establish a *prima facie* case of obviousness have not been met. First, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

> All words in a claim must be considered in judging the patentability of that claim against the prior art.

In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) (emphasis added). Applicant maintains that Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest the claimed compositions having specifically recited SEQ ID NOS. In particular, Brooks et al. does not teach or suggest the claimed antibody comprising a variable region amino acid sequence referenced as SEQ ID NOS:2 and 4 or encoding nucleic acids (SEQ ID NOS:1 and 3). Thus, in contrast to Applicant's claims, which specifically recite SEQ ID NOS, Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest any nucleotide or amino acid sequences of LM609 or LM609 CDR-grafted antibodies, let alone the sequences specifically recited in the claims. As such,

Brooks et al., alone or in combination with known methods of gene cloning, does not teach or suggest all of the claim limitations.

Secondly in regard to establishing a *prima facie* case of obviousness, there must be a reasonable expectation of success. In re Longi 759 F.2d 887, 225 U.S.P.Q. 645 (Fed Cir. 1985) In re Merck & Co., Inc. 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986); In re O'Farrell 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). For the reasons set forth in the previous responses, Brooks et al., alone or in combination with known methods of gene cloning, fails to provide a reasonable expectation of success. In particular, as set forth in the response mailed June 7, 2000, and as corroborated in the Declaration by Dr. Huse filed as Exhibit 2 in the response mailed June 7, 2000, the cloning of variable region nucleotide sequences from a hybridoma cell was not routine due to the difficulties associated with cloning authentic cDNA sequence encoding the monoclonal antibody expressed by a hybridoma. Therefore, based on the lack of description in Brooks et al. for any nucleotide or amino acid sequence of LM609 and the known difficulties of cloning authentic cDNA encoding a monoclonal antibody expressed in a hybridoma cell, Applicant contends that one skilled in the art would have had no reasonable expectation of success for obtaining the claimed compositions having specifically recited SEQ ID NOS.

Further in regard to the alleged obviousness of the nucleic acids encoding the parental non-human LM609 antibody and

the generation of LM609 CDR-grafted antibodies, Applicant has set forth in the previous responses mailed March 3, 1998, December 9, 1998, September 20, 1999, and June 7, 2000, the controlling case law to which the facts of the above-identified application are properly applied in determining the issue of obviousness of the claimed nucleotide sequences. Briefly, the question of whether a nucleotide sequence is rendered obvious by a prior art disclosure of the corresponding amino acid sequence has been examined by the Federal Circuit in In re Deuel, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). The Deuel court framed the inquiry in terms of whether the combination of a prior art reference teaching a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein, may render DNA and cDNA molecules encoding the protein *prima facie* obvious. In contrast to the prior art reference cited in In re Deuel, the Brooks et al. patent, U.S. Patent No. 5,753,230, fails to provide any nucleotide or amino acid sequence of LM609. The Deuel court clearly stated its rationale that:

> [O]ne could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.

Id. at 1558, 34 U.S.P.Q.2d at 1215. Applicant maintains that, for the reasons described above, conception of the claimed compositions having specifically recited SEQ ID NOS did not occur

until the nucleotide sequence of LM609 heavy and light chain variable regions was cloned, determined and used to generate the LM609 CDR-grafted antibodies and encoding nucleic acids. In contrast, Brooks et al., alone or in combination with known methods of gene cloning, fails to provide any nucleotide or amino acid sequence of LM609 and therefore provides no indication of conception of the claimed compositions having specifically recited SEQ ID NOS. In accordance with the reasoning of the Deuel court, such a lack of disclosure cannot be considered sufficient to render obvious the claimed compositions having specifically recited SEQ ID NOS.

Moreover, the Examiner's argument that methodology exists which allegedly permits one skilled in the art to obtain the nucleotide sequence of an antibody based on the existence of constant regions ignores the clear mandate of Deuel:

> We today affirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed cDNAs.... A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out.

Id. at 1559, 34 U.S.P.Q.2d at 1215-1216. Applicant maintains that the lack of disclosure in Brooks et al. of any nucleotide or amino acid sequence corresponding to LM609 or any of the claimed CDR-grafted antibodies cannot render the claimed compositions

obvious. At best, Brooks et al. may provide a general incentive, but such a general incentive is insufficient to render obvious the claimed compositions having specifically recited SEQ ID NOS.

Regarding the assertion in the Office Action on page 8 with respect to a "modification thereof that does not change the encoded amino acid sequence," Applicant points out that this phrase is not recited in the claims of the present application. Furthermore, Applicant maintains that the recited functional fragments of the claimed antibodies would not have been obvious in view of the cited art.

In summary, Applicant respectfully maintains that the claimed antibodies and nucleic acids having the structural features specifically recited in the claims as SEQ ID NOS are unobvious over Brooks et al., alone or in view of the known art for cloning immunoglobulin genes from a hybridoma cell. Therefore, the rejection of the claims under 35 U.S.C. § 103 is respectfully requested to be withdrawn.

Double Patenting Rejection

Claims 1-18 and 26-31 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-8, 15-26, 33-42, 56 and 57 of copending application serial number 08/791,391. Claims 1-18 and 26-31 also stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 56-97

of copending application serial number 09/016,061 and claims 1-20 and 25-33 of copending application serial number 09/339,922. Applicant respectfully requests that these provisional grounds of rejection be deferred until there is an indication of allowable subject matter.

Applicant also respectfully requests that the request for showing the requirements under 37 C.F.R. § 1.78(c) be deferred until there is an indication of allowable subject matter. Applicant also respectfully requests clarification of the paragraph regarding same since it is unclear why the cited applications, serial Nos. 09/016,061 and 09/339,922, which were filed after the filing date of the above-identified application, would qualify as prior art under 35 U.S.C. § 102(f) or (g).

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

September 14, 2001
Date

David A. Gay
Registration No. 39,200
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122
USPTO CUSTOMER NO. 23601